B-type natriuretic peptide (BNP) is a hormone responsible for numerous physiological effects such as natriuresis and vasodilation. The active BNP hormone and an inactive metabolite N-terminal proBNP (NT-proBNP) are released in equimolar amounts by ventricular cardiomyocytes in response to hemodynamic stress. Abundant data are available to support the clinical use of BNP and NT-proBNP as biomarkers for aiding in the diagnosis and prognosis of patients presenting with signs and symptoms of heart failure. Also, recent evidence has emerged to support the prognostic value of BNP and NT-proBNP in acute coronary syndromes (ACS).

BNP and N-terminal proBNP: clinical utilisation in diagnosis, prognosis, and risk stratification

by Dr H. Azzazy and Prof. R. Christenson

Coronary heart disease (CHD) is among the leading causes of global morbidity and mortality. CHD now accounts for almost one half of all deaths in the developed world and 25% in the developing world. In the US alone 61 million individuals live with CHD, of which 4.7 million are symptomatic heart failure (HF) patients. The annual cost of HF in the US is estimated at $56 billion. Guidelines for heart failure management, published by the American College of Cardiology (ACC) and the American Heart Association (AHA), define four stages of heart failure. These are coronary artery disease together with risk factors such as hypertension, diabetes mellitus and family history (Stage A); previous myocardial infarction, heart valve disease, and preclinical ventricular dysfunction (Stage B); structural heart disease with overt signs and symptoms of HF (Stage C); and preterminal HF with marked symptoms at rest despite maximal therapy (Stage D) [1]. The document also emphasised the importance of diagnosis and treatment of the early stages of HF. Interest has emerged in the diagnostic ability of the natriuretic peptides to identify patients with Stage B and Stage C HF as well as for patient prognosis.

Recent studies have confirmed the clinical usefulness of BNP and NT-proBNP assays not only for the stratification of patients with HF, but also for the diagnosis and prognosis of HF in symptomatic patients presenting to the Emergency Department, as well as for the determination of prognosis in ACS patients. The task force of the European Society of Cardiology for the Diagnosis and Treatment of Chronic HF recommended that a cardiac natriuretic peptide assay should be included in the first step of the algorithm for the diagnosis of HF [2].

**Biochemistry and physiology of cardiac natriuretic peptides**

The cardiac natriuretic peptides include atrial natriuretic peptide (ANP) and BNP, and their related metabolic peptides. The natriuretic peptides are released in response to increased hemodynamic stress such as fluid overload and increased wall tension, and they are involved in regulating blood pressure, sodium excretion and fluid balance. Other physiologic actions of ANP/BNP include inhibition of the sympathetic nervous system, counterbalance of the renin-angiotensin-aldosterone system and inhibition of the endothelins, vasopressin, and cytokines; the natriuretic peptides also appear to play a role in the inhibition of ventricular and vascular hypertrophy and remodelling. The natriuretic peptides have beneficial effects on endothelial dysfunction subsequent to atherosclerosis such as blunting of shear stress, regulation of coagulation and fibrinolysis, and inhibition of platelet coagulation [3]. BNP has been found to be more predictably associated with disease than ANP, so development of ANP clinical assays has not been pursued for routine clinical use.

BNP is synthesised inside myocytes as a 108 amino acid precursor molecule. Upon stimulus for release, this precursor is enzymatically cleaved into the active 32-amino acid BNP hormone and a metabolically inactive N-terminal protein having 76 amino acids (NT-proBNP). Key characteristics of BNP and NT-proBNP are shown in Table 1. The plasma concentration of BNP is controlled by the rate of synthesis and release, and balanced by clearance mechanisms that include active receptors found in vascular endothelium, smooth muscle, heart, and kidney, enzymatic degradation in circulation and receptor-mediated endocytosis. NT-proBNP is cleared solely by glomerular filtration.

**Current BNP and NT-proBNP assays**

Over the past 5 years several BNP and NT-proBNP immunoassays have become commercially available. Clinical studies have documented the clinical utility of such assays for the differential diagnosis of dyspnea, risk stratification of patients with HF and ACS, and detection of left ventricular systolic and/or diastolic dysfunction [4, 5]. Table 2 shows a list of BNP and NT-proBNP assays. Five assays are currently approved by the US Food and Drug Administration (FDA) for aiding the diagnosis of heart failure. Most of the early clinical and basic research studies for BNP utilised the Shionogi test. This test received FDA approval in 2003 and is now available in automated system platforms [Table 2]. The Triage BNP was first introduced in 2000. It employs only one fluorescently labelled polyclonal antibody and an immobilised monoclonal antibody that recognises the ring structure of BNP. This test, with a turnaround time of 15 minutes, has been used by most recent clinical
with lean individuals (BMI <25 kg/m²), obese individuals (BMI ≥30 kg/m²) had higher odds of having low BNP plasma levels (multivariable-adjusted odds ratio: men 2.51 [95% CI: 1.71-3.68]; women 1.84 [95% CI: 1.32-2.58]). In addition to implications for the use of BNP levels in patient care, such low circulating levels of BNP may contribute to the susceptibility of obese individuals to hypertension and related disorders such as left ventricular hypertrophy.

Diabetes
In a preliminary study, plasma NT-proBNP levels were measured in subjects from primary care centres that had no overt heart disease: 253 patients with type 2 diabetes and 230 matched controls. NT-proBNP levels were higher in type 2 diabetics without overt heart disease (361 pmol/L compared to the controls (303 pmol/L (P<0.001)). The authors suggested that measurement of NT-proBNP, if paired with cystatin C to estimate glomerular filtration rate, might be used to identify diabetic patients at risk for ventricular dysfunction and who could benefit from an echocardiographical examination [7].

Clinical utility of B-type Natriuretic Peptides
BNP in diagnosis of symptomatic HF patients
The value of BNP and NT-proBNP in aiding the diagnosis of HF in patients presenting with dyspnea is well established. The "Breathing Not Properly" study was the first large-scale multicentre, multinational, prospective study that evaluated the use of BNP for diagnosis of dyspnea [8]. BNP levels were measured in 1586 patients who had been admitted to the ED with acute dyspnea. The ED physicians were blinded to BNP results and asked to assess the probability of patients having HF. In addition, two other cardiologists, also blinded to BNP levels, were asked to review all clinical data and standardise scores to produce a clinical diagnosis for each patient. Compared to clinical history, physical measurements and other laboratory results, BNP levels were found to be the most accurate predictor of HF diagnosis. BNP levels were elevated in patients in subsequent HF (675 pg/mL) compared to those with non-cardiac dyspnea (110 pg/mL). A BNP cut-off of 100 pg/mL differentiated HF from other causes of dyspnea (90% sensitivity and 76% specificity). A BNP cutoff of 50 pg/mL had a negative predictive value of 96%.

A study was made comparing the utility of BNP and NT-proBNP in the diagnosis of HF in 205 patients presenting to the emergency department with acute dyspnea [9]. Diagnostic classification of the two assays correlated well (r = 0.902, P < 0.0001). The best sensitivities and specificities were achieved at a BNP value of 96%.

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Table 3. Selected studies evaluating BNP and NT-proBNP assays as prognostic risk markers in HF patients.

Table 2. Current BNP and NT-proBNP assays.

<table>
<thead>
<tr>
<th>Assay</th>
<th>Technology</th>
<th>Total %CV range</th>
<th>Dynamic range (pg/mL)</th>
<th>Antigens recognised &amp; antibodies used</th>
<th>Study</th>
<th>Protocol</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shionogi BNP</td>
<td>IBMA</td>
<td>-</td>
<td>0-4000</td>
<td>Antigens: BNP 1-32, 3-10, proBNP 1-108 Capture antibody: Shionogi tag structure Detection antibody: Shionogi CODIS terminus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abbott AntiYM BNP</td>
<td>Microparticle-based immunoassay</td>
<td>6.5-9.4</td>
<td>0-4000</td>
<td>Antigens: BNP 1-32, 3-10, proBNP 1-108 Capture antibody: Sciroc (tag structure) Detection antibody: Sciroc (CODIS terminus)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bayer Sedia Contour BNP (ACS 180)</td>
<td>Chemiluminescent sandwich immunoassay</td>
<td>3.4-7</td>
<td>0-5000</td>
<td>Antigens: BNP 1-32, 3-10, proBNP 1-108 Capture antibody: Shionogi tag structure Detection antibody: Shionogi CODIS terminus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roche Elecsys NT-proBNP (Dade Behring Dimension, Mason, OH)</td>
<td>Electro-chemi-luminescent immunometric assay (Immunoassay)</td>
<td>3.6-5.8</td>
<td>0-35,000</td>
<td>Antigens: NT-proBNP 1-76, BNP 1-108, truncated NT-proBNP Capture antibody: Roche (antigen terminus, n-1-211) Detection antibody: Roche (a 39-50)</td>
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<tr>
<td>Biosite Triline BNP (Beckman, Accus, Accus, 2, Symmetry LS, UniCel DXP)</td>
<td>Point-of-care immunoassay (two-site chemi-luminescent immunoassay)</td>
<td>9.9-12.2 (21.6-8.7)</td>
<td>0-5000 (10-1000)</td>
<td>Antigens: BNP 1-32, 3-10, proBNP 1-108 Capture antibody: Sciroc (tag structure) Detection antibody: Biosite (antigen terminus)</td>
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<td></td>
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</tbody>
</table>

Table 3. Selected studies evaluating BNP and NT-proBNP assays as prognostic risk markers in HF patients.
NT-proBNP will evolve into very important prognostic risk markers in ACS patients. So these biomarkers can be used for risk assessment and prognosis of ACS comes. Haemodynamic stress and ventricular wall tension increases BNP and NT-proBNP and HF. Further, these patients will also have a greater number of other adverse outcomes that can cause progressive LV dilatation and dysfunction with development of HF function. It is logical that patients having increased haemodynamic stress during dynamic stress, reduced cardiac performance and symptoms of ventricular dysfunction. In frank MI patients necrosis also causes increased haemodynamic ischaemia results in local myocardial dysfunction and increased haemodynamic consequences that covers unstable angina through frank myocardial infarction (MI) indicate that the natriuretic peptides reflect the heart’s hormonal activities, and are clinical indicators of haemodynamic stress due to any cause. Plasma levels are affected by age, gender, renal function, and other physiological variables. Thus, as with any biomarker, BNP and NT-proBNP measurements should be considered equivalent for the diagnosis of HF in symptomatic patients presenting to the ED, the prognosis of symptomatic patients, as well as the risk stratification of patients with ACS.

**Table 4. BNP and NT-proBNP as prognostic and risk markers in ACS patients.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Protocol</th>
<th>Marker(s)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richards et al. [Circulation. 2003;107:2786-92]</td>
<td>A cohort of 666 pts with AMI, followed for 3 years</td>
<td>BNP</td>
<td>NT-proBNP</td>
</tr>
<tr>
<td>Morrow et al. [J Am Coll Cardiol. 2003;41:1264-72]</td>
<td>Substudy of TACTICS Randomized controlled trial 1676 patients, 6 months follow up</td>
<td>BNP</td>
<td>In patients with BNP=80 pg/mL, there was increased risk of death at 7 days (2.5% vs. 0.7%) and 6 months (6.4% vs. 1.8%)</td>
</tr>
<tr>
<td>Jernberg et al. [J Am Coll Cardiol 2003;42:1909-16]</td>
<td>Substudy of FRISC II Randomized controlled trial 755 patients, 2 year follow up</td>
<td>NT-proBNP</td>
<td>Relative risk for mortality was 4.1 for patients in the third NT-proBNP tertile (95% CI: 2.4-7.2) [non-invasive group] Relative risk for mortality was 3.5 for patients in the third tertile NT-proBNP (95%CI: 1.8-6.8) [invasive group]</td>
</tr>
<tr>
<td>James et al. [Circulation. 2003;108:275-81]</td>
<td>Substudy of GUSTO IV Randomized controlled trial 6809 patients, 1 year follow up</td>
<td>NT-proBNP</td>
<td>Relative risk for mortality was 10.6 in highest vs. lowest quartile of BNP</td>
</tr>
<tr>
<td>H瀤esen et al. [Circulation. 2004;110:3206-12]</td>
<td>1791 NTSE ACS pts. Death &amp; MI were recorded within 30 days</td>
<td>NT-proBNP</td>
<td>In TnT-negative pts, NT-proBNP identified a subgroup of high risk pts (OR, 5.9 [95% CI: 2.6-13.3], P&lt;0.001) In pts with low NT-proBNP baseline levels, a rise in NT-proBNP over 72 hrs (&gt;270 ng/L) was linked to an adverse 30-day outcome (OR: 24 [95% CI: 8.4-68.5], P&lt;0.001)</td>
</tr>
<tr>
<td>Gélvani et al. [Circulation. 2004;110:128-34]</td>
<td>Marker was measured on admission in 1756 pts with ACS and ECG evidence of myocardial ischaemia 30-day outcome was death (occurred in 6.4% of pts)</td>
<td>NT-proBNP</td>
<td>Compared with the lowest quartile, pts in the second, third, and fourth quartiles had a relative risk of subsequent death of 2.94 [95% CI: 1.15-7.52], 5.32 [95% CI: 2.19-12.91], and 11.5 [95% CI: 4.9-26.87]; NT-proBNP was independently associated with death in a logistic regression model which included clinical variables, ECG, and TnT in pts with or without persistent ST-segment elevation</td>
</tr>
</tbody>
</table>

**Conclusions**

The natriuretic peptides reflect the heart’s hormonal activities, and are clinical indicators of haemodynamic stress due to any cause. Plasma levels are affected by age, gender, renal function, and other physiological variables. Thus, as with any biomarker, BNP and NT-proBNP measurements should be considered equivalent for the diagnosis of HF in symptomatic patients presenting to the ED, the prognosis of symptomatic patients, as well as the risk stratification of patients with ACS.

**References**


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